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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,460	08/19/1998	HERMAN WALDMANN	1283-36	7809

7590 03/01/2004

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/125,460	WALDMANN ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,26-29,31-35,37-58,60-69 and 71-75* is/are pending in the application.

4a) Of the above claim(s) *18,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29,31-35,37-58,60-69 and 73-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 36 and 59 have been canceled.

Claims 26 has been amended.

2. Claims 18, 71-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 28.

3. Claims 26-29, 31-35, 37-58, 60-69 and 73-75 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains a NEW GROUND of rejection.

Claim Objection

6. Claim 26 is objected to because it appears to have a typographical error in the last line which recites "an L or H chain or an unrelated antibody" which should read "an L or H chain of an unrelated antibody".

appropriate correction is needed

Rejections Withdrawn

7. The rejection of claim 59 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily

available to the public; (2) reproducible from the written description is withdrawn in view of the amendment to the claim.

8. The rejection of claims 26-29, 31-69 and claims 73-75 under 35 U.S.C. 103(a) as being unpatentable over Isaacs et al (Therapeutic Immunology 1:303-312, 1994, IDS #5) and further in view of Carter et al (U.S. Patent 6,054,297, CON to 1992) and Riechmann et al (Nature 332:323, 1988, IDS #5) is withdrawn in view of the new ground of rejection.

The following is a NEW GROUND of rejection/Response to Arguments

Claim Rejections - 35 USC § 103

9. Claims 26-29, 31-35, 37-58, 60-69 and 73-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaacs et al (Therapeutic Immunology 1:303-312, 1994, IDS #5) and further in view of Carter et al (U.S. Patent 6,054,297, CON to 1992) and Rudikoff et al (PNAS 79:1979-1983, 1982).

The claims are summarized as a method of producing a non-cell binding antibody for inducing immunological tolerance to a therapeutic antibody by identifying one or more amino acids in a CDR and modifying the amino acid to produce a non-cell binding antibody wherein the non-cell binding antibody has reduced affinity to 1% of the therapeutic antibody, comprises one epitope of the therapeutic antibody, induces immunological tolerance to the therapeutic antibody, has variable domains with 99%

identity to the therapeutic antibody and is not a mixed molecule. Further claimed is the amino acids are modified by site directed mutagenesis, has the same constant region, a fragment of the antibody, recovering the antibody, has affinity for CD52, humanized frameworks, no binding in an ELISA at 10,000 times the maximum concentration of the therapeutic antibody.

Isaacs et al each a method of avoiding anti globulin responses to a therapeutic antibody by producing a non-cell binding antibody. The antibody binds CD52 and Isaacs teach that non-cell binding variants of therapeutic mabs could be usefully exploited to generate therapeutic unresponsiveness to any clinically useful mab. Isaacs et al does not teach human frameworks, fragments, or variable regions that are greater than 90% identity to the variable domains in the therapeutic antibody. These deficiencies are made up for in the teachings of Carter et al and Rudikoff et al.

Carter et al teach production of humanized antibodies, fragments of antibodies (column 8) and three dimensional models to identify residues that are involved with antigen binding and are responsible for affinity in a positive as well as negative sense and in some instances the effect of decreased binding might be desired and CDR residues are directly and most substantially involved and influence antigen binding (see column 9, lines 35-60).

Rudikoff et al teach a single amino acid substitution in a CDR eliminated binding of the antibody to the antigen (see Table 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a non cell binding antibody for

inducing immunological tolerance by identifying a CDR residue and mutating the residue to produce a non-cell binding antibody with essentially no binding ability to antigen in view of Isaacs et al, Carter et al, and Rudikoff et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a non cell binding antibody for inducing immunological tolerance by identifying a CDR residue and mutating the residue to produce a non-cell binding antibody with essentially no binding ability to antigen in view of Isaacs et al, Carter et al, and Rudikoff et al because Isaacs et al teach production and the advantages of producing non-cell binding antibodies for inducing immunological tolerance to any therapeutic antibody. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a non cell binding antibody for inducing immunological tolerance by identifying a CDR residue and mutating the residue to produce a non-cell binding antibody with essentially no binding ability to antigen in view of Isaacs et al, Carter et al, and Rudikoff et al because Carter teach that one can humanize an antibody for reducing an immune response or avoiding the antiglobulin response and the antibodies can be altered to lower the affinity. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a non cell binding antibody for inducing immunological tolerance by identifying a CDR residue and mutating the residue to produce a non-cell binding antibody with essentially no binding ability to antigen in view of Isaacs et al, Carter et al, and Rudikoff

et al because Rudikoff et al teach that one only needs to alter one amino acid in the binding site of an antibody to eliminate binding to the antigen.

One of ordinary skill in the art at the time the invention was made would have been motivated to select non-cell binding antibody variants, including fragments, of therapeutic antibodies, including anti-CD52 antibody, to generate therapeutic unresponsiveness to clinically useful antibodies by a variety of recombinant means available to the ordinary artisan at the time the invention was made, as evidenced by Carter et al. The claimed method is obvious because Carter teach humanization and this is a method of inducing tolerance to an antibody when administered to a patient, i.e. reduce the antiglobulin response. If the only residue that is altered in a humanized antibody is the residue in the CDR as taught by Rudikoff et al to produce a non-cell binding antibody, then it is obvious that the frameworks and constant regions would be 100% identical to those in the therapeutic humanized antibody. In addition, it is well known that the CDR residues influence binding as evidenced from Rudikoff et al and Carter et al even teach that one can reduce affinity in some circumstances and in view of Isaacs et al who teach non-binding variants, it would have been obvious to alter the CDR residues as taught by Rudikoff et al. Therefore the claimed limitations encompassing substitutions and alterations in sequences as well as reduced affinity would have been expected properties of selecting for non-cell binding variants of therapeutic antibodies at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 2/12/04 has been carefully considured but is deemed not to be persuasive. The response states that Isaccs method can only be achieved by administration of a combination of two non-cell binding mixed molecules antibodies (see page 13-14 of response). In response to this argument, the claims do not require that only one non-cell binding antibody be used or produced. In fact the claims are directed to producing a non-cell binding antibody that has 4 properties which the combination of references above would obviously produce. The response further states that Carter teach replacing each CDR with a neutral (human) CDR for improving humanization (see page 14). In response to this Carter teach retention of the mouse CDRs and replacement of frameworks with human frameworks (as required in claims 60-62). The response states that Carter et al is concerned with the host being tolerant of human immunoglobulin frameworks and is unable to respond against it and this is different from the object of the invention which is concerned with reprogramming the human host not to respond to the antibody and the technique can be applied to any protein not just antibodies as in Carter and Carter teaches away from the invention (see page 14 of response). In response to this argument, the examiner does not understand how the invention is different from humanization when humanization is used to make an antibody tolerant and the instant method does the same. Both make the host tolerant of the antibody. With regard to the speculation that the claimed method can be used for

any protein not just antibodies, the claims only require an antibody. The response states that Professor Waldmann stated that the invention is surprising and unexpected because one would not have expected that having a variable domain of greater that 90% to the therapeutic antibody would have non-cell binding and tolerance (see page 15). In response to this argument, it is obvious that elimination of binding can be made by reducing a single amino acid in a CDR as evidenced from Rudikoff et al and that the non-cell binding antibody would still be tolerant because it is still a humanized antibody as evidenced from Carter who humanized antibodies for the purpose of being tolerant.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832